43. (New) The method of claim 10 wherein the human has one or more of the following conditions: abnormal serum lipid levels, hypertension, cigarette smoking, diabetes mellitus, obesity, physical inactivity, hyperhomocysteinemia and chlamydia pneumoniae infection.

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44. (New) The method of claims 1, 2, 3, 4, 5, or 6 wherein the atherosclerosis is in the common iliac arteries, internal iliac arteries, external iliac arteries, or the pulmonary arteries.

REMARKS

The Claimed Invention

Upon entry of the present amendment, Claims 1-31 and 43-44 are pending in the subject application. Claims 32-42 have been canceled without prejudice to Applicant's right to pursue the subject matter of the canceled claims in related applications. Applicants fully reserve their rights to prosecute the subject matter of any canceled claim in one or more continuation, continuation-in-part, or divisional applications. Claim 10 has been amended to recite multiple dependencies in the alternative. Claim 43 has been added as a dependant claim of amended claim 10 and contains the limitations set in the original claim 10. Claim 44 has been added to more particularly point out the invention. Support for claim 44 can be found in Table I on page 22. No new matter is added by these amendments. Claims 3,6 and 19 have been withdrawn from consideration as being directed to non-elected subject matter. Claims 1, 2, 4, 5, 7-18, and 20-31 of the instant application relate to methods of treating or preventing atherosclerosis and restenosis in a human or animal using an effective amount of a TNF-α inhibitor. In certain embodiments, the effective amount of a TNF-α inhibitor is about 300 mg/kg/day or less.

Rejection Under 35 U.S.C. § 103(a)

Claims 1, 2, 4, 5, 7-18, and 20-31 are rejected as unpatentable under 35 U.S.C. § 103(a) over United States Patent No. 5,635,517 to Muller et. al. ("Muller"). The Examiner contends that Muller teaches a method of reducing TNF-α levels and that unregulated TNF-α productions has been implicated in a number of disease states. Although Applicants do not

disagree with this statement, Applicants respectfully submit that this contention is insufficient to maintain the rejection of obviousness as further discussed below.

As the Examiner is likely aware, in order to properly determine a *prima facie* case of obviousness, an Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." Manual of Patent Examining Procedure §2142 (8th ed., August 2001). This is important, as "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art." *Id.* Three basic criteria must then be met: first, there must be some suggestion or motivation to modify or combine the cited references; second, there must be a reasonable expectation of success; and third, the prior art references must teach or suggest all the claim limitations. *Id.* at § 2143.

As stated above, Applicant claims a method of treating or preventing atherosclerosis and restenosis in a human or animal using an effective amount of a TNF-α inhibitor. The Examiner admits that "Muller does not expressly teach utilizing 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline for the prevention of atherosclerosis or resteneosis" (Office Action, at Page 4). The Examiner contends that the disclosure of congestive heart failure in Muller at column 3, lines 59-65 would make it obvious to one of skill in the art to modify the reference of Muller for the treatment of atherosclerosis and restenosis. Applicant respectfully disagree because congestive heart failure, atherosclerosis and restenosis are each distinct diseases with distinct etiologies and are each treated with different therapies.

Congestive heart failure is defined by the American Heart Association as "heart failure in which the heart is unable to maintain an adequate circulation of blood in the bodily tissues or to pump out the venous blood returned to it by the veins." *Webster's Ninth New Collegiate Dictionary*, 1989, at page 276. Atherosclerosis is "characterized by irregularly distributed lipid deposits in the intima of large and medium-sized arteries, causing narrowing of arterial lumens." *Stedman's Medical Dictionary*, 27th Ed., 2000, at page 162. Restenosis is defined as "the narrowing of a structure following the removal or reduction of a previous narrowing." *Id.* at page 1556. Clearly each disorder is distinct. Indeed, this is confirmed by the differences in the treatment of each disease. In particular, congestive heart failure is commonly treated by the use of diuretics and vasodilators which act to expand arteries so as to increase blood flow without reducing cardiac output. Unlike congestive heart failure,

atherosclerosis and restenosis are most commonly treated by the use of drugs to reduce the plasma lipoprotein levels including antioxidants, niacin and estrogen which act to remove arterial plaque and other blockages. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th Ed., 1996 880-881.

The mere statement that the compounds of Muller can be used to treat congestive heart failure does not provide an adequate suggestion of Applicants' novel method of treating or preventing atherosclerosis or restenosis. Muller's statement, at best, provides an invitation to experiment. Muller does not provide a reasonable expectation of success. *In re Fine,* 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). As the Examiner knows, "obvious to try" is not the proper legal standard. *In re O'Farrel* 853 F.2d 894, 903, 57 USLW 2147, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988). In sum, this unsupported allegation fails to provide the requisite legal suggestion plus reasonable expectation of success. Applicant therefore respectfully submits that claims 1, 2, 4, 5, 7-18, and 20-31 are not obvious over Muller. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection of claims 1, 2, 4, 5, 7-18, and 20-31 under 35 U.S.C. §103(a).

Conclusion

Applicants respectfully request that the above remarks and accompanying documents be entered in the present application file. Applicants also respectfully request withdrawal of the outstanding rejections. An early allowance of the present application is respectfully requested.

No fee is believed due. However, if the Examiner determines that any fee is due, please charge the required fee to Pennie & Edmonds LLP Account No. 16-1150.

Respectfully submitted,

Date: February 20, 2003

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Anthony M. Insogna (Reg. No.)
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

By: Natalie Di Ceglie
Reg. No. 51,615

EXHIBIT A

United States Patent Application Serial No. 09/734,460, Filed December 11, 2000

Marked-Up Version of Amended Claims, Indicating Insertions and Deletions

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10. (Amended) The method of <u>any one of</u> claims 1, 2, <u>or</u> 3 wherein the mammal is a human [subject and is] at risk for complications of atherosclerosis [and has one or more of the following conditions: abnormal serum lipid levels, hypertension, cigarette smoking, diabetes mellitus, obesity, physical inactivity, hyperhomocysteinemia and chlamydia pneumoniae infection].

<u>43. (New) The method of claim 10 wherein the human has one or more of the following conditions: abnormal serum lipid levels, hypertension, cigarette smoking, diabetes mellitus, obesity, physical inactivity, hyperhomocysteinemia and chlamydia pneumoniae infection.</u>

<u>44. (New) The method of claims 1, 2, 3, 4, 5, or 6 wherein the atherosclerosis is in the common iliac arteries, internal iliac arteries, external iliac arteries, or the pulmonary arteries.</u>

EXHIBIT B

United States Patent Application Serial No. 09/734,460, Filed December 11, 2000

Pending Claims Incorporating Amendments Made Herein

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1. A method of preventing atherosclerosis in a mammal comprising administering to a mammal an effective amount of a TNF-α inhibitor selected from the group consisting of:

cyano and carboxy derivatives of substituted styrenes; cyclic imides; cycloalkyl amides and cycloalkyl nitrites; aryl amides; 1-oxo-2-(2,6-dioxo-3-fluoropiperidin-3yl) isoindolines and 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidine-3-yl) isoindolines; tetra substituted 2-(2,6-dioxopiperdin-3-yl)-1-oxoisoindolines; imide/amide ethers and alcohols; succinimides and maleimides; 1-oxo-and 1,3 dioxo-2-(2,6-dioxopiperidin-3-yl) isoindolines substituted with amino in the benzo ring; imido and amido substituted alkanohydroxamic acids; substituted phenethylsulfones substituted to the phenyl group with an oxoisoindine group; 1-Oxo and 1,3 dioxo-2-(2,6-dioxopiperidin-3yl) isoindolines; non-polypeptide cyclic amides; imido and amido substituted alkanohydroxamic acids; and substituted phenethylsulfones.

2. A method of preventing atherosclerosis in a mammal comprising administering to a mammal an effective amount of a TNF-α inhibitor selected from the group consisting of: 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline, 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline and 3-(3,4-dimethoxyphenyl)-3-(1-oxisoindolin-2-yl)propionamide.

3. A method of preventing atherosclerosis in a mammal comprising administering to a mammal an effective amount of a TNF-α inhibitor selected from the group consisting of thalidomide, its analogs, its hydrolysis products, its metabolites and its precursors.

4. A method of treating atherosclerosis in a mammal comprising administering to a mammal in need thereof an effective amount of a TNF-α inhibitor selected from the group consisting of:

cyano and carboxy derivatives of substituted styrenes; cyclic imides; cycloalkyl amides and cycloalkyl nitrites; aryl amides; 1-oxo-2-(2,6-dioxo-3-fluoropiperidin-3yl) isoindolines and 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidine-3-yl) isoindolines; tetra substituted 2-(2,6-dioxopiperdin-3-yl)-1-oxoisoindolines; imide/amide ethers and alcohols; succinimides and maleimides; 1-oxo-and 1,3 dioxo-2-(2,6-dioxopiperidin-3-yl) isoindolines substituted with amino in the benzo ring; imido and amido substituted alkanohydroxamic acids; substituted phenethylsulfones substituted to the phenyl group with an oxoisoindine group; 1-Oxo and 1,3 dioxo-2-(2,6-dioxopiperidin-3 yl) isoindolines; non-polypeptide cyclic amides; imido and amido substituted alkanohydroxamic acids and substituted phenethylsulfones.

5. A method of treating atherosclerosis in a mammal comprising administering to a mammal in need thereof an effective amount of a TNF-α inhibitor selected from the group consisting of: 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline; 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline; and 3-(3,4-dimethoxyphenyl)-3-(1-oxisoindolin-2-yl)propionamide.

6. A method of treating atherosclerosis in a mammal comprising administering to a mammal in need thereof an effective amount of a TNF-α inhibitor selected from the group consisting of thalidomide, its analogs, its hydrolysis products, its metabolites and its precursors.

7. The method of claims 1, 2, 3, 4, 5, or 6 wherein the atherosclerosis is in the aorta, coronary artery, mesenteric arteries, or carotid arteries.

8. The method of claims 1, 2, 3, 4, 5, or 6 wherein the atherosclerosis is in the renal arteries.

9. The method of claims 1, 2, 3, 4, 5, or 6, wherein the mammal is a human.

10. (Amended) The method of any one of claims 1, 2, or 3 wherein the mammal is a human at risk for complications of atherosclerosis.

11. The method of claim 10 wherein the subject and has not undergone surgical vascular intervention.

12. The method of claims 1, 2, 3, 4, 5, or 6 wherein approximately .01 mg/kg to 300 mg/kg of body weight is administered per day.

13. The method of claim 12 wherein approximately 0.1 mg/kg to 100 mg/kg of body weight is administered per day.

14. The method of claim 13 wherein approximately 0.5 mg/kg to 50 mg/kg of body weight is administered per day.

15. The method of claim 14 wherein approximately 1.0 mg/kg to 10 mg/kg of body weight is administered per day.

16. The method of claim 1, 2, 3, 4, 5, or 6 wherein the method of administration is oral.

17. A method of inhibiting or preventing restenosis in a mammal comprising administering to a mammal in need thereof an effective amount of a TNF-α inhibitor selected from the group consisting of:

cyano and carboxy derivatives of substituted styrenes; cyclic imides; cycloalkyl amides and cycloalkyl nitrites; aryl amides; 1-oxo-2-(2,6-dioxo-3-fluoropiperidin-3yl) isoindolines and 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidine-3-yl) isoindolines; tetra substituted 2-(2,6-dioxopiperdin-3-yl)-1-oxoisoindolines; imide/amide ethers and alcohols (for example 3-Phthalimido-3-(3',4'-dimethoxypheryl)propan-1-ol); succinimides and maleimides; 1-oxo-and 1,3 dioxo-2-(2,6-dioxopiperidin-3-yl) isoindolines substituted with amino in the benzo ring; imido and amido substituted alkanohydroxamic acids; substituted phenethylsulfones substituted to the phenyl group with an oxoisoindine group; 1-Oxo and 1,3 dioxo-2-(2,6-dioxopiperidin-3 yl) isoindolines; non-polypeptide cyclic amides; imido and amido substituted alkanohydroxamic acids; and substituted phenethylsulfones.

18. A method of inhibiting or preventing restenosis in a mammal comprising administering to a mammal in need thereof an effective amount of a drug selected from the group consisting of: 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline; 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline; and 3-(3,4-dimethoxyphenyl)-3-(1-oxisoindolin-2-yl)propionamide so that restenosis is prevented or reduced.

~~19.~~ A method of inhibiting or preventing restenosis in a mammal comprising administering to a mammal in need thereof an effective amount of a TNF-α inhibitor selected from the group consisting of thalidomide, its analogs, its hydrolysis products, its metabolites and its precursors so that restenosis is prevented or reduced.

20. The method of claim 17 wherein approximately .01 mg/kg to 300 mg/kg of body weight administered per day.

21. The method of claim 20 wherein approximately 0.1 mg/kg to 100 mg/kg of body weight is administered per day.

22. The method of claim 21 wherein approximately 0.5 mg/kg to 50 mg/kg of body weight is administered per day.

23. The method of claim 22 wherein approximately 1.0 mg/kg to 10 mg/kg of body weight is administered per day.

24. The method of claims 17, 18 or 19 wherein the treatment begins prior to surgical intervention.

25. The method of claim 24 wherein treatment begins prior to surgical intervention and is continued for about 4 to 12 weeks after the surgical intervention.

26. The method of claim 24 wherein the treatment begins about 12 hours or less prior to scheduled intervention.

27. The method of claim 25 wherein the treatment begins about 12 hours or less prior to scheduled intervention.

28. The method of claim 24 wherein the surgical intervention is percutaneous coronary intervention, percutaneous transluminal coronary angioplasty, carotid percutaneous transluminal angioplasty coronary by-pass grafting or coronary angioplasty with stent implantation.

29. The method of claim 24 wherein the surgical intervention is renal angioplasty, peripheral percutaneous transluminal intervention of the iliac, femoral or popliteal arteries or surgical intervention using impregnated artificial grafts.

30. The method of claims 17, 18, or 19 wherein the surgical intervention is unscheduled and treatment begins at the time of surgery.

31. The method of claims 17, 18, or 19 wherein the surgical intervention is unscheduled and treatment begins at the time of surgery and is discontinued about 4 to 12 weeks after the surgical intervention.

43. (New) The method of claim 10 wherein the human has one or more of the following conditions: abnormal serum lipid levels, hypertension, cigarette smoking, diabetes mellitus, obesity, physical inactivity, hyperhomocysteinemia and chlamydia pneumoniae infection.

44. (New) The method of claims 1, 2, 3, 4, 5, or 6 wherein the atherosclerosis is in the common iliac arteries, internal iliac arteries, external iliac arteries, or the pulmonary arteries.